DOI: https://doi.org/10.17816/DD633487

Comparative role of radiological imaging methods in biochemical recurrence of prostate cancer

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ABSTRACT

Biochemical recurrence of prostate cancer following radical treatment, including radical prostatectomy and radiotherapy, occurs in approximately 25%–50% of patients. However, the clinical course and prognosis of the disease vary among patients and depend on several factors. Consequently, the optimal diagnostic and treatment methods for patients with biochemical recurrence of prostate cancer remains debatable. Biochemical recurrence may be caused by local recurrence, metastatic dissemination, or a combination of these processes. Recently, approaches to the diagnosis and treatment of patients with biochemical recurrence of prostate cancer have undergone significant changes with the introduction of more accurate diagnostic methods. This article provides a review of the current capabilities of radiological imaging and radionuclide diagnostic methods in visualizing local recurrence and metastases in patients with biochemical recurrence of prostate cancer.

Keywords: prostate cancer; biochemical recurrence; prostate-specific membrane antigen; combined positron emission tomography and computed tomography; combined positron emission tomography and magnetic resonance imaging.

To cite this article:
Rostovtseva TM, Dolgushin MB, Karalkina MA, Koroid OA, Sinitsyn VE. Comparative role of radiological imaging methods in biochemical recurrence of prostate cancer. *Digital Diagnostics.* 2025;6(1):46–62. DOI: https://doi.org/10.17816/DD633487

Received: 17.06.2024 **Accepted:** 24.10.2024

ECO•VECTOR

DOI: https://doi.org/10.17816/DD633487

Сравнительная роль методов лучевой диагностики при биохимическом рецидиве рака предстательной железы

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АННОТАЦИЯ

Биохимический рецидив рака предстательной железы возникает приблизительно в 25–50% случаев среди пациентов после его радикального лечения, как после радикальной простатэктомии, так и после лучевой терапии. Однако клиническое течение и прогноз заболевания у разных пациентов с биохимическим рецидивом рака предстательной железы существенно отличаются и зависят от целого ряда факторов. В связи с этим оптимальный алгоритм диагностики и лечения пациентов с биохимическим рецидивом рака предстательной железы до настоящего времени является предметом научных споров. Причиной биохимического рецидива рака предстательной железы может быть как локальный рецидив, так и метастатическая диссеминация, а также сочетание этих процессов. В последние годы подходы к диагностике и лечению пациентов с биохимическим рецидивом рака предстательной железы претерпели существенные изменения в связи с внедрением в клиническую практику более точных методов диагностики. В статье представлен обзор литературных данных о современных возможностях методов лучевой и радионуклидной диагностики при визуализации местного рецидива и метастазов рака предстательной железы у пациентов с биохимическим рецидивом.

Ключевые слова: рак предстательной железы; биохимический рецидив; простатоспецифичный мембранный антиген; совмещённая позитронно-эмиссионная и компьютерная томография; совмещённая позитронно-эмиссионная и магнитно-резонансная томография.

Как цитировать:
Ростовцева Т.М., Долгушин М.Б., Каралкина М.А., Короид О.А., Синицын В.Е. Сравнительная характеристика методов лучевой диагностики при биохимическом рецидиве рака предстательной железы // Digital Diagnostics. 2025. Т. 6, № 1. С. 46–62. DOI: https://doi.org/10.17816/DD633487

Рукопись получена: 17.06.2024 **Рукопись одобрена:** 24.10.2024 **Опубликована online:** 22.01.2025

DOI: https://doi.org/10.17816/DD633487

前列腺癌生化复发的放射学诊断方法比较研究

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摘要

前列腺癌的生化复发发生在大约25%–50%的患者中，这些患者在接受前列腺癌的根治性治疗后，包括根治性前列腺切除术和放射治疗。然而，生化复发前列腺癌患者的临床过程和预后差异显著，具体情况取决于多个因素。因此，生化复发前列腺癌的最佳诊断和治疗方案至今仍是学术界争论的焦点。生化复发的原因可能是局部复发、转移性扩散或两者结合。近年来，随着更加精确的诊断方法的临床应用，生化复发前列腺癌患者的诊断和治疗方法发生了显著变化。本文回顾了当前关于生化复发前列腺癌患者中局部复发和转移灶影像学的放射学和核素影像学方法的文献数据。

关键词：前列腺癌；生化复发；前列腺特异性膜抗原；电子发射计算机断层扫描；电子发射磁共振成像。

引用本文：
Rostovtseva TM, Dolgushin MB, Karalkina MA, Koroid OA, Sinitsyn VE. 前列腺癌生化复发的放射学诊断方法比较研究. *Digital Diagnostics.* 2025;6(1):46–62. DOI: https://doi.org/10.17816/DD633487

收到：17.06.2024 **接受：**24.10.2024 **发布日期：**22.01.2025

INTRODUCTION

In Russia, prostate cancer (PCa) ranks first in cancer incidence and third in cancer-related mortality among the male population, accounting for 17% and 8.9%, respectively. The incidence and mortality rates have continued to increase over the past decade [1]. Serum prostate-specific antigen (PSA) levels are a key parameter for monitoring patients after treatment. Biochemical recurrence occurs in 25%–50% of patients following radical prostatectomy or radiation therapy, with a sustained risk for >10 years [2]. Without intervention, clinical progression develops in 24%–34% of cases. Notably, the interval between the onset of biochemical markers and clinical manifestations is 5–8 years, and the 15-year PCa-specific mortality rate reaches 6% [3–7].

Biochemical recurrence after radical prostatectomy is defined as PSA > 0.2 ng/mL, with 0.4 ng/mL threshold indicating metastatic progression [8]. For patients treated with radiation therapy, biochemical recurrence is defined as an increase in PSA > 2 ng/mL above the post-treatment nadir (Phoenix definition by RTOG-ASTRO) [9]. Patients undergoing minimally invasive treatments such as high-intensity focused ultrasound or cryotherapy may also experience biochemical recurrence; however, specific thresholds for these patients remain undefined [10].

Biochemical recurrence is not a direct indicator of PCa-specific or overall mortality. According to several studies, biochemical recurrence may precede clinical progression by an average of 8 years post-prostatectomy and 7 years post-radiotherapy [11, 12].

Biochemical recurrence may result from locoregional metastasis to lymph nodes, bones, or other organs or a combination thereof. From a clinical perspective, the probability of metastatic disease being the cause of biochemical recurrence is higher in patients with high-grade tumors (Gleason score ⩾ 8), seminal vesicle invasion, pelvic lymph node involvement, or early biochemical recurrence, within 6 months post-prostatectomy or 1 year following radiation therapy. Conversely, local recurrence is more likely in patients with less-aggressive tumors (Gleason score < 8); absence of seminal vesicle invasion, but presence of prostatic capsular invasion or positive surgical margins; and delayed biochemical recurrence ⩾1 year post-radiotherapy or ⩾3 years post-prostatectomy [13, 14]. A PSA doubling time <12 months after prostatectomy or <18 months after radiotherapy is associated with high risk of disease progression. A doubling time <3 months is linked to rapid clinical manifestation, regardless of biochemical recurrence timing [15, 16]. Moreover, the time from radical prostatectomy to biochemical recurrence correlates with PCa-specific mortality in high-risk patients; however, it has no impact in low-risk groups [15].

Therefore, high-risk patients exhibit increased rates of metastasis and PCa-specific mortality. Criteria defining this group include:

- Gleason score of 8–10, seminal vesicle invasion, or lymph node metastasis
- PSA doubling time <3 months or biochemical recurrence occurring within 6 months post-prostatectomy or 1 year post-radiotherapy

These patients require earlier initiation of treatment [8, 17, 18]. In contrast, low-risk patients include those with:

- Gleason score <8
- PSA doubling time >12 months post-prostatectomy and >18 months post-radiotherapy [19].

“Ideal” candidates for active surveillance include the following patients:

- Aged > 80 years
- With tumors graded 6–7 on Gleason score or prognostic grade group 1–2 by the International Society of Urological Pathology
- Experiencing late-onset biochemical recurrence (>5 years)
- With prolonged PSA doubling time (>12 months) and PSA <0.5 ng/mL at biochemical recurrence
- With significant comorbidities and competing mortality risk [20].

TREATMENT APPROACHES

According to the 2020 European Association of Urology (EAU) guidelines, the treatment of PCa recurrence after radical prostatectomy include salvage radiotherapy to the prostate bed or beyond, continuous or intermittent endocrine therapy, and surveillance [19]. The efficacy of salvage radiotherapy depends on the presence or absence of distant metastases and is greater when initiated early at lower PSA levels [21–23].

Recent studies have confirmed the rationale for early salvage radiotherapy in patients with biochemical recurrence of PCa after radical prostatectomy. In a 2009 study, Boorjian et al. [24] revealed that early initiation of salvage radiotherapy in patients with biochemical recurrence reduced the risk of systemic progression by 75%. In the 2020 RADICALS-RT trial, the 5-year biochemical recurrence-free survival among patients who received salvage radiotherapy at PSA levels of 0.1–0.2 ng/mL was 88% [25]. According to Stish et al. [21], if treatment in patients with biochemical recurrence was initiated before PSA reached 0.5 ng/mL, the 5- and 10-year recurrence-free survival rates were 60% and 40%, respectively. In a 2008 study by Wiegel et al. [26], salvage radiotherapy initiated at a median PSA of 0.33 ng/mL led to undetectable PSA in 60% of patients over the next 40 months. Trock et al. [27] reported that among patients with biochemical or local recurrence and PSA doubling time <6 months, prostate cancer-specific survival was threefold higher in those who received salvage radiotherapy than in those who did not, over a 6-year follow-up. Moreover, radiotherapy initiated ⩾2 years after biochemical recurrence had no effect on prostate cancer-specific survival.

The EAU recommends that patients with high-risk features (Gleason score ⩾ 8 or PSA doubling time <1 year) and PSA > 0.4 ng/mL after radical prostatectomy should undergo salvage radiotherapy. For low-risk patients (Gleason score < 8 and PSA doubling time > 1 year), active surveillance remains a viable strategy [16].

For patients who develop biochemical recurrence of PCa after radiation therapy, treatment includes radical prostatectomy, cryotherapy, continuous or intermittent hormone therapy, high-intensity focused ultrasound, and observation [28]. Some patients may be eligible for radical treatment [19], which requires accurate localization of the tumor focus and metastases prior to planning.

The optimal treatment timing and modality for patients with biochemical recurrence after radical prostatectomy or radiation therapy remains debatable. On the one hand, there is a need to delay clinical progression; on the other hand, overtreatment may occur in patients who may never experience progression. Adjuvant therapy after radical prostatectomy and local radiotherapy following external beam radiation are reserved for patients at high risk of local recurrence or progression; they are not recommended for low-risk patients because of the potential adverse effects of radiation and hormonal therapies [16].

DIAGNOSIS

The effectiveness of recurrent PCa treatment is significantly higher when therapy is initiated at low PSA levels <0.5 ng/mL [21–23]. Adequate treatment planning requires accurate localization of recurrent lesions and a precise assessment of tumor burden at the earliest possible stage of PCa. At PSA < 1 ng/mL, the sensitivity of conventional imaging modalities, such as ultrasound, multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), and positron emission tomography (PET) with ^{11}C-choline or ^{18}F-methylcholine is limited [29].

In a meta-analysis of 23 studies by Abuzallouf et al. (2004) [30], bone scintigraphy identified osseous metastases in 2.3% of patients with PSA < 10 ng/mL, 5.3% with PSA of 10–20 ng/mL, and 16.2% with PSA of 20–59 ng/mL. Furthermore, MDCT detected bone metastases in 6.4% of patients with organ-confined disease and in 49.5% of those with locally advanced PCa. In a study by O'Sullivan et al. (2015) [31], the sensitivity and specificity of MDCT for detecting bone metastases in patients with PCa were 56% and 74%, respectively.

The sensitivity of MDCT in detecting local recurrence or lymph node metastases was low:

- Local recurrence: ⩽14% [32]
- Lymph node metastases at PSA > 25 ng/mL: 10% [33]
- Micrometastases in lymph nodes: ⩽ 1% [19].

In a study by Abuzallouf et al. [30], the sensitivity, specificity, and positive and negative predictive values of MDCT for detecting lymph node metastases in PCa were 16%, 100%, 85%, and 100%, respectively.

The sensitivity of ^{11}C- and ^{18}F-choline PET is strongly PSA-dependent. Krauze et al. [34] reported lesion detection in 36% of patients with PSA < 1 ng/mL, 43% with PSA < 2 ng/mL, and 73% with PSA > 3 ng/mL. Moreover, the short half-life of ^{11}C-choline (20 minutes) poses a limitation for its clinical use, in addition to the ligand's low specificity.

MRI is widely used for detecting PCa local recurrence. However, currently, no standardized scoring system comparable to Prostate Imaging Reporting and Data System (PI-RADS) exists for local recurrence. Most protocols follow a multiparametric MRI (mpMRI) scheme, similar to that used in primary PCa diagnosis [35]. Radical prostatectomy involves complete removal of the prostate gland and seminal vesicles and, in some cases, pelvic lymph node dissection. In post-radical prostatectomy patients, the prostate gland and seminal vesicles are not visualized on MRI; however, the vesicourethral anastomosis between the repositioned bladder neck and extraprostatic urethral segment can be identified. This area appears as fibrous tissue with low signal intensity on all sequences, without diffusion restriction or early contrast enhancement. Residual seminal vesicles may be present, with or without fibrotic changes [36]. A characteristic local recurrence manifests as a soft-tissue lesion with intermediate signal intensity on T2-weighted images (T2WI), diffusion restriction, and early contrast enhancement (Fig. 1). These signal features resemble those of primary PCa lesions [37]. Diffusion-weighted imaging (DWI) interpretation may be complicated by surgical suture artifacts. Combined analysis of T2-weighted imaging, dynamic contrast-enhanced sequences, and DWI allows for more confident differentiation between local recurrence and inflammatory changes, residual prostatic tissue, and fibrotic and granulation tissue [38].

According to several studies, in most cases, local recurrence is visualized in the perianastomotic region and less frequently in the retrovesical space or at the bladder neck in the area of the seminal vesicles [39–41]. Dirix et al. [41] identified local PCa recurrence in the peri-anastomotic area in 50% of cases, seminal vesicle bed in 40%, and retrovesical space in 9%. The sensitivity of MRI in detecting local recurrence after radical prostatectomy reaches 85%–90% in patients with PSA > 1 ng/mL, tumor volume > 1 mL, or palpable lesion [42, 43]. However, MRI performance diminishes at lower PSA levels requiring intervention. In a study, Dirix et al. [41] reported that mpMRI detected local recurrence in only 25% of patients with biochemical recurrence, with mean PSA levels of 0.3 ng/mL in the entire cohort and 1.4 ng/mL in those with MRI-detectable lesions. Buergy et al. [44] did not identify any local recurrence in patients with PSA < 0.3 ng/mL using 3T mpMRI. Notably, these patients later demonstrated a favorable response to radiation therapy, as evidenced by a decrease in PSA. In a 2015 study by Hernandes et al. [37], retrospective analysis of mpMRI in patients with biochemical recurrence after radical prostatectomy (mean PSA: 0.38 ng/mL)

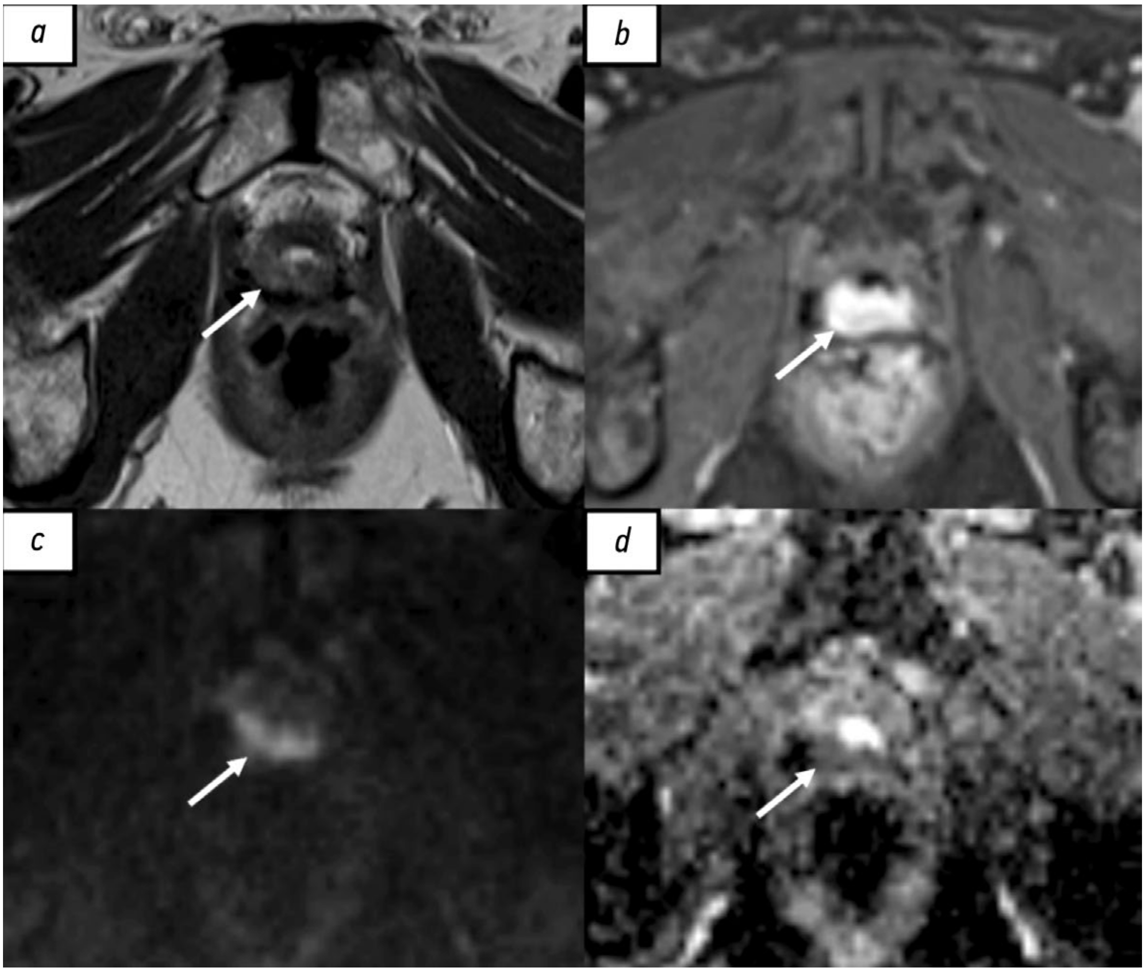

Fig. 1. Recurrent prostate cancer in the vesicourethral anastomosis region after radical prostatectomy, original observation. *a*, Axial T2-weighted magnetic resonance image showing an area of intermediate signal intensity at the posterior aspect of the vesicourethral anastomosis (*arrow*); *b*, axial fat-suppressed T1-weighted image showing contrast enhancement at the same location (*arrow*); *c*, axial diffusion-weighted image; and *d*, apparent diffusion coefficient map. Diffusion restriction at the posterior aspect of the vesicourethral anastomosis (*arrows*).

revealed local recurrence in 38% of cases. Sharma et al. [45] proposed that the absence of mpMRI evidence of local recurrence in such patients is an independent negative predictor of radiation therapy response, supplementing the Stephenson nomogram derived from a cohort of 1881 patients with PCa.

Lymph node metastases are evaluated using MDCT and MRI based on size, shape, contour, and internal architecture. In a study by Hövels et al. [46], the sensitivity of these modalities in detecting nodal metastases in PCa was 42% for CT and 39% for MRI, with specificity around 82%. The sensitivity of whole-body diffusion-weighted MRI (DW-MRI) for detecting distant metastases surpasses that of bone scintigraphy, even when combined with MDCT of the chest, abdomen, and pelvis [47]. Its diagnostic performance in detecting pulmonary and bone metastases is comparable to that of ^{11}C-choline PET [48].

Whole-body mpMRI combines anatomical and at least two functional MRI pulse sequences. It includes a T1-weighted Dixon sequence, a short tau inversion recovery T2-weighted sequence, DWI with multiple b-values, apparent diffusion

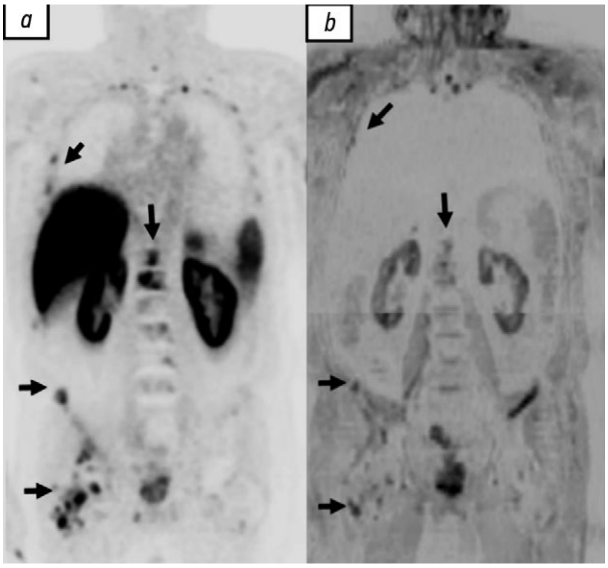

Fig. 2. Multiple bone metastases in a patient with prostate adenocarcinoma (Gleason score: 3+4), original observation. *a*, Positron emission tomography using ^{18}F-prostate-specific membrane antigen-1007; and *b*, inverted whole-body diffusion-weighted image.

coefficient maps, fat fraction maps in some cases, and dynamic contrast-enhanced imaging and magnetic resonance spectroscopy. Despite the superior sensitivity of whole-body mpMRI in detecting local recurrence and bone and visceral metastases compared with DWI alone, its effectiveness remains limited in identifying lymph node metastases (Fig. 2) [49, 50].

Ultrasound has limited sensitivity for detecting local recurrence, which also affects the diagnostic yield of vesicourethral anastomosis biopsies under ultrasound guidance: 40%–70% in patients with PSA > 1 ng/mL and ≤45% in those with PSA < 1 ng/mL [51].

Thus, in several patients with biochemical recurrence and low PSA levels, conventional imaging fails to identify the source of recurrence.

The introduction of PET with prostate-specific membrane antigen (PSMA) ligands into clinical practice has substantially improved the diagnosis and management of biochemical recurrence of PCa.

PSMA is a transmembrane glycoprotein that was first isolated from PCa cells in 1987. Low-level PSMA expression is found in the membranes of normal prostatic epithelial cells and benign prostatic hyperplasia. In contrast, PSMA expression is increased in 90% of PCa cases [52], particularly in aggressive castration-resistant subtypes, local recurrence, and metastatic disease (Fig. 3). Moreover, PSMA expression is occasionally observed in the endothelium of non-prostatic solid tumors, which is associated with neoangiogenesis [53].

Agents labeled with gallium (^{68}Ga) and fluorine (^{18}F) are the most commonly used among radiopharmaceuticals targeting PCa cells. In 2020–2021, the US Food and Drug Administration approved ^{68}Ga-PSMA-11 (gallium-^{68} gozetotide) and ^{18}F-piflufolastat, as well as ^{18}F-flotufolastat in 2023. These agents demonstrated comparable diagnostic performance in phase 3 clinical trials. Currently, several alternative radiopharmaceuticals are undergoing clinical evaluation, including ^{18}F-PSMA-1007,

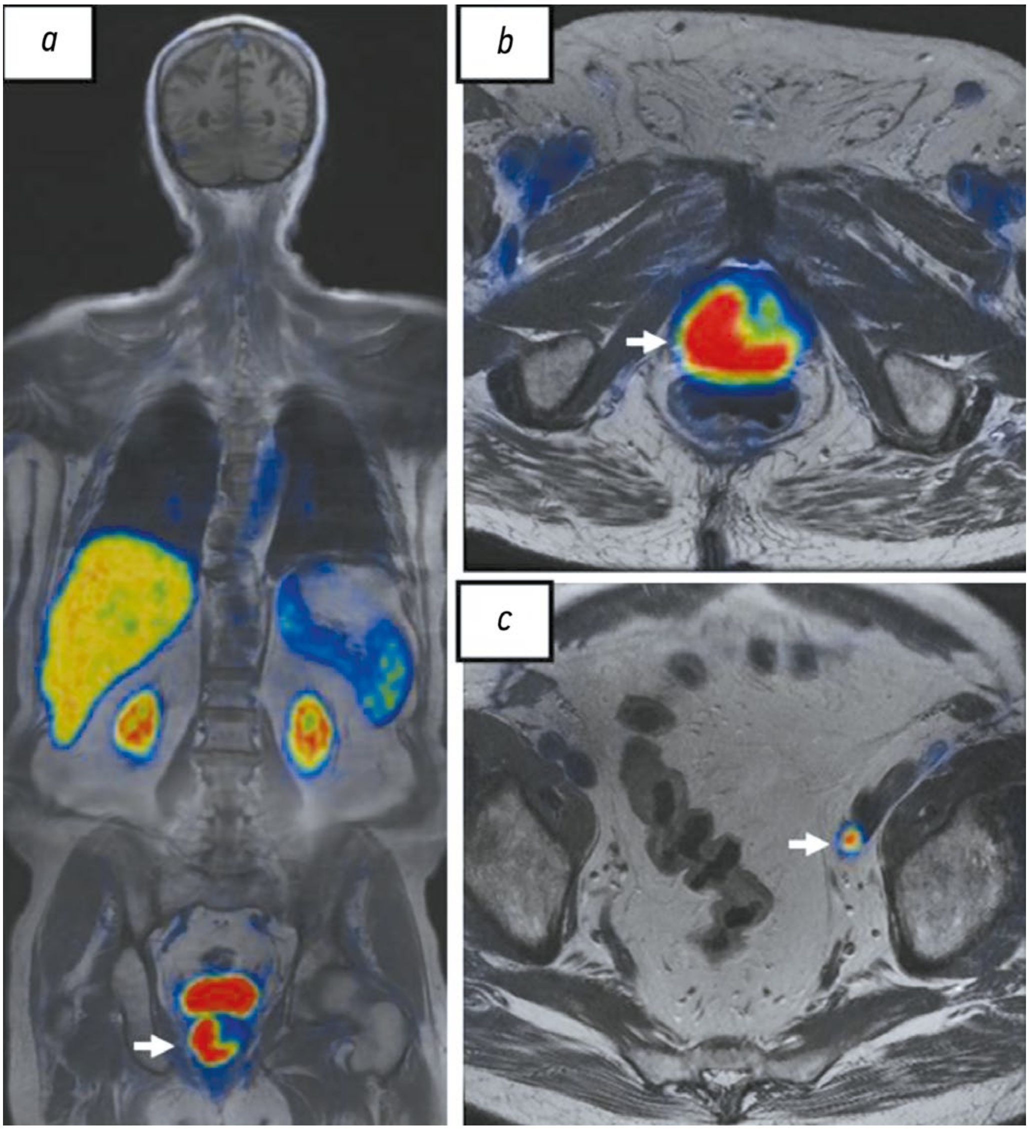

Fig. 3. Whole-body hybrid positron emission tomography/magnetic resonance imaging with ^{18}F-prostate-specific membrane antigen-1007, original observation. *a*, *b*, Prostate tumor with subtotal involvement of the right lobe extending into the left lobe (*arrows*); and *c*, hyperexpression of ^{18}F-prostate-specific membrane antigen-1007 in a metastatic iliac lymph node (*arrow*).

^{18}F-fluorine-labeled compound (^{18}F-CTT1057), ^{68}Ga-PSMA-R2, and copper-labeled PSMA (^{64}Cu-SAR-bisPSMA). Among these, no substantial diagnostic advantages have been established, except for promising data with ^{64}Cu-SAR-bisPSMA [54–58]. Whole-body PET dosimetry with ^{68}Ga-PSMA-11 and ^{18}F-piflufolastat is similar (effective dose: 4.4 and 4.3 mSv, respectively, for 370 MBq administered) and comparable to ^{18}F-FDG PET. No clinically significant adverse events were reported during clinical trials of either agent. Transient changes in blood pressure and heart rate occurred, but did not require treatment [59]. ^{18}F has a longer half-life than ^{68}Ga (110 vs. 68 min); additionally, ^{18}F demonstrates a shorter positron range and higher positron yield. Primarily, ^{18}F-labeled agents are hepatically excreted, whereas ^{68}Ga-labeled agents are renally excreted [60]. These properties confer ^{18}F-PSMA tracers with higher spatial resolution and fewer artifacts from bladder activity [61–63]. When PSMA PET imaging is performed prior to planned PSMA-targeted radionuclide therapy with lutetium (^{177}Lu) or actinium (^{225}Ac) compounds, it is crucial to note that criteria for assessing PSMA expression activity in PCa metastases, as predictors of treatment efficacy, have been established only for ^{68}Ga-labeled tracers [64].

The sensitivity and specificity of PSMA PET significantly exceed those of different imaging. In a study by Fendler et al. (2019) [65], detection rates with ^{68}Ga-PSMA-11 PET in patients with biochemical recurrence of PCa were 38% with PSA <0.5 ng/mL, 57% with PSA of 0.5–1 ng/mL, 85% with PSA of 1–2 ng/mL, 86% with PSA of 2–5 ng/mL, and 97% with PSA > 5 ng/mL. Higher PSA levels were associated with multiple and extrapelvic lesions. Even among patients with PSA < 0.5 ng/mL, extrapelvic disease was found in approximately one-third of cases. Similar findings were reported by Boreta et al. [66] and Calais et al. [67] in 2019 and 2018, respectively, with mean PSA levels of 0.4 and 0.48 ng/mL. In these studies, PET with 68Ga-PSMA-11 detected recurrence in 53% and 49% of cases. Furthermore, in 38% and 20% of cases, respectively, the tumor focus was outside the prostatectomy bed and thus outside the planned radiation field; thus, the treatment strategy was changed. The most common extraprostatic sites were mesorectal lymph nodes (23%) and bones (44%). Ignatova et al. [68] used ^{68}Ga-PSMA PET/CT and reported detection rates of 36% for PSA < 0.2 ng/mL, 69% for 0.2–0.4 ng/mL, 84% for 0.4–0.6 ng/mL, and 88% for 0.6–0.8 ng/mL. Sawicki et al. [69] found that PSMA PET/CT was 4.3 times more sensitive for detecting metastases than whole-body DW-MRI. Meshcheryakova et al. [70] demonstrated that ^{18}F-PSMA-1007 PET/CT revealed structural recurrence in 77.8% of patients who had negative ^{18}F-choline PET/CT findings.

Among patients who experience biochemical recurrence after external beam radiotherapy, the main diagnostic goal is to identify those eligible for salvage therapy: radical prostatectomy, cryotherapy, brachytherapy, or high-intensity focused ultrasound [71]. In these patients, pelvic mpMRI and PSMA PET are highly sensitive for detecting local recurrence [72]. MRI protocols are generally similar to those used for primary PCa detection. When MRI and PSMA PET findings concur, the possibility of local recurrence exceeds 97%, potentially eliminating the need for biopsy [73].

The sensitivity of single-photon emission computed tomography (SPECT) using PSMA labeled with technetium-99m (^{99m}Tc and ^{99m}Tc-PSMA) in detecting PCa local recurrence and metastases is lower than that of PET/CT. In a study by Albalooshi et al. (2020) [74], patients with PCa underwent both ^{68}Ga-PSMA-11 PET/CT and ^{99}mTc-PSMA SPECT within a 2-month period. PET/CT detected twice as many lesions with pathologic PSMA expression. Lawal et al. [75] found that ^{99}mTc-PSMA SPECT missed >70% of lesions identified on ^{68}Ga-PSMA-11 PET/CT in the same patient population, including >80% of pathologically altered lymph nodes smaller than 10 mm in diameter. Nevertheless, ^{99}mTc-PSMA SPECT is considered a more affordable and accessible alternative to PSMA-ligand PET/CT and employed for radiation therapy planning and radionuclide therapy when PET is unavailable.

The introduction of more sensitive diagnostic techniques for detecting recurrent PCa led to a change in treatment strategy in up to 70% of evaluated patients [43, 76]. Treatment plans are often adjusted toward more aggressive interventions, but also including targeted and metastasis-directed therapies [20]. These changes resulted in improved recurrence-free survival [77], overall survival [78], and delayed initiation of androgen deprivation therapy, improving patients' quality of life [79].

PET/CT and PET/MRI provide comparable diagnostic accuracy in detecting primary PCa [80], although PET/MRI provides superior assessment of extracapsular extension and seminal vesicle invasion [80, 81]. Both modalities are used in identifying lymph node, bone, and visceral metastases and local recurrence [82–84].

Despite their similarities, PET/CT and PET/MRI have several key differences. Radiation exposure from PET/MRI is up to 80% lower than from PET/CT (approximately 5 mSv), although the scan time is substantially longer, requiring approximately 45 min for whole-body imaging [80]. PET/MRI simultaneously acquires PET and MRI data, whereas PET/CT does so sequentially. This hybrid modality combines high-resolution anatomical imaging of soft tissues, particularly of the pelvic structures, using T2- and T1-weighted sequences. The sensitivity of DWI and specificity of PSMA-ligand PET enable simultaneous assessment of structural alterations, diffusion characteristics, vascularization, and PSMA expression within pathologic areas. This integrated assessment is beneficial for evaluating bone involvement, considering the limited sensitivity of MDCT for detecting bone metastases in patients with biochemical recurrence and PSA < 5 ng/mL. However, PET/MRI is inferior to PET/CT in evaluating pulmonary lesions. A principal limitation of PET/MRI is its less accurate attenuation correction, which hinders assessment of PSMA expression in pathologic lesions compared with PET/CT and requires additional mathematical adjustments to interpret changes in standardized uptake values correctly.

In a study by Guberina et al. (2020) [85], PET/CT and PET/MRI with ^{68}Ga-PSMA-11 were performed in 93 patients with biochemical recurrence of PCa following radical prostatectomy. PET/MRI was conducted immediately after MDCT. The median PSA was 1.64 ng/mL (range: 0.59–4.7 ng/mL). PET/MRI detected 148 of 150 PSMA-positive lesions identified by PET/CT (excluding 2 lymph nodes) and revealed 11 additional lesions, including 5 metastatic lymph nodes and 6 local recurrence sites. The difference in sensitivity between hybrid modalities was attributed to variations in PET component sensitivity, not between CT and MRI. In this study, the higher sensitivity of PET/MRI (98.8% vs. 93.2%) may be attributed to the Lorentz force acting on the positron within a high-intensity magnetic field, causing it to spiral. This reduces the distance between the positron emission and annihilation points, improving spatial resolution (Fig. 4) [86]. Similar findings were reported by Lutje et al. [87] in 2017: 14 local lesions and 23 pathologically altered lymph nodes were identified in 25 patients with biochemical recurrence using PET/MRI with ^{68}Ga-HBED-CC-PSMA. Additionally, PET/CT with ^{68}Ga-HBED-CC-PSMA in the same cohort identified 14 local recurrences and 20 PET-positive lymph nodes. No difference was observed in sensitivity between the modalities for the detection of bone metastases. Two studies demonstrated that the higher sensitivity of PET/MRI with ^{68}Ga-PSMA-11 compared with PET/CT using the same radiotracer (67.9% vs. 64.2%) in detecting local recurrence among 53 patients with biochemical recurrence of PCa was attributable to the MRI component. This improvement was due to superior delineation of pelvic structures, enabling tumor tissue detection despite the presence of bladder-related artifacts [83, 88].

Incorporating hybrid imaging techniques such as PET/CT and PSMA PET/MRI into clinical practice is reflected in current clinical guidelines. The latest edition of the EAU clinical guidelines in 2021 [89] recommends the use of PSMA-ligand PET/CT or PET/MRI in patients who are at high risk for biochemical recurrence of PCa. Similarly, the most recent guidelines of the National Comprehensive Cancer Network (NCCN, 2024) [90] and European Society for Medical Oncology (2022) [91] recommend these imaging modalities for high- and intermediate-risk patient groups. The NCCN guidelines indicate that the sensitivity and specificity of PSMA-ligand PET significantly surpass those of conventional imaging such as CT and MRI for detecting micrometastases. Therefore, preliminary conventional imaging is not mandatory before or alongside PSMA-ligand PET/CT or PET/MRI, for initial staging or in biochemical recurrence [90].

Notably, the false-positive rate of PSMA-ligand PET can reach up to 10% [92]. Increased PSMA expression has been found in tumors of the stomach, colon, kidneys, thyroid, and breast and in inflammatory sites such as osteomyelitis and areas of healing fractures. Moreover, PSMA overexpression has been reported in benign lesions such as hemangiomas and fibrous dysplasia (Fig. 5) [53].

In a retrospective study by Chen et al. (2020) [93], PET/CT with ^{68}Ga-PSMA-11 was performed in 62 patients with PCa who had a solitary extraprostatic focus of ^{68}Ga-PSMA-11 overexpression in a rib. The mean SUV$_{max}$ of these lesions was 3.02. In 61 of 62 patients (98.4%), no biochemical recurrence

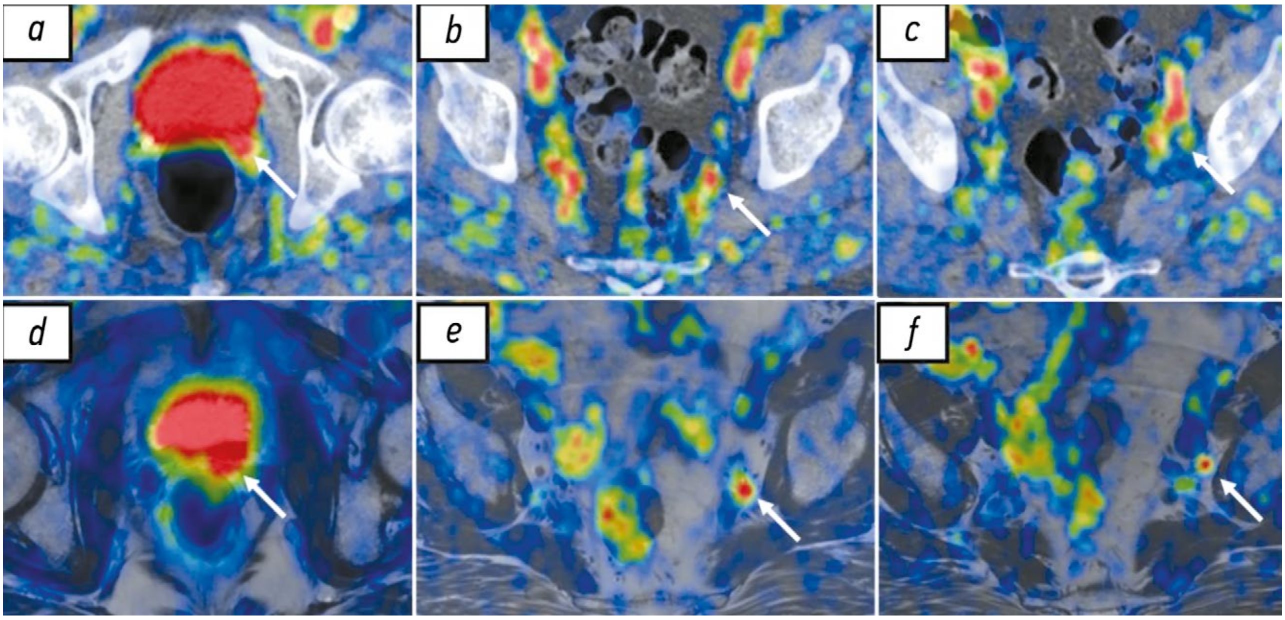

Fig. 4. Hybrid positron emission tomography/computed tomography with ^{68}Ga-prostate-specific membrane antigen (*a*, *b*, and *c*) and hybrid positron emission tomography/magnetic resonance imaging with ^{18}F-prostate-specific membrane antigen-1007 (*d*, *e*, *f*) in a patient with recurrent prostate cancer after radical prostatectomy, original observation. *a*, *d*, local recurrence at the left vesicourethral anastomosis (*arrows*); *b*, *c*, increased prostate-specific membrane antigen expression in a non-enlarged left internal iliac lymph node; *c*, absence of prostate-specific membrane antigen expression (*arrow*); and *f*, visualization of increased prostate-specific membrane antigen expression (*arrow*).

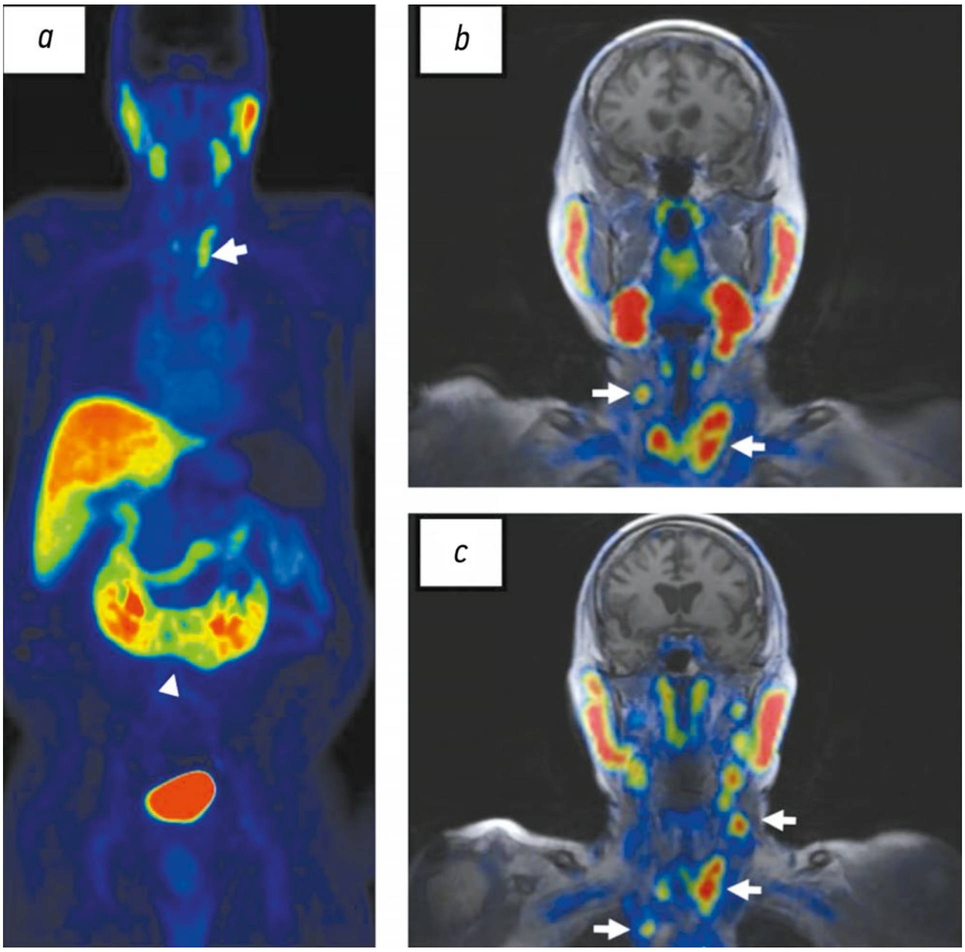

Fig. 5. Whole-body hybrid positron emission tomography/magnetic resonance imaging (PET/MRI) with ^{18}F-prostate-specific membrane antigen-1007 (18F-PSMA-1007), original observation. Hyperexpression of ^{18}F-PSMA-1007 in papillary thyroid carcinoma and its cervical lymph node metastases (*arrows*) in a patient with prostate adenocarcinoma (incidental finding). *a*, The arrowhead indicates a horseshoe kidney (incidental finding).

was observed after treatment, and no signs of lesion progression were detected in patients who underwent follow-up imaging. In three cases, rib lesion biopsies were performed: two revealed benign histologic findings, and one yielded an indeterminate result. In 11 patients (17.7%), the area of PSMA overexpression corresponded to consolidated fracture sites. Notably, one lesion (1.6%) initially appeared benign but subsequently enlarged, and new osteosclerotic foci developed. In 69.4% of cases, the SUV$_{max}$ value in benign lesions (2.21) exceeded that in the malignant lesion. Therefore, PET findings should be interpreted in comparison with MRI or MDCT results and prior diagnostic studies. Moreover, a small subset of PCa does not exhibit increased PSMA expression, making the combined interpretation of PET findings and mpMRI data essential [88, 94].

Several scoring systems have been proposed to standardize the interpretation of PSMA-ligand PET/CT and PET/MRI. The most widely used among them are the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria developed in 2018 [80], which represent a TNM-based classification adapted for molecular imaging (miTNM), and the PSMA-RADS system [95], an analog of the PI-RADS scale. The PROMISE criteria can be applied for the initial diagnosis of PCa and in patients with biochemical recurrence. The intensity of PSMA expression (miPSMA expression score) in this system is graded based on the standardized average SUV (SUV$_{mean}$) on a 0–3 scale:

- 0: PSMA expression below blood pool
- 1: higher than blood pool but lower than liver parenchyma
- 2: higher than liver parenchyma but lower than salivary glands
- 3: higher than salivary glands.

For radiotracers eliminated via the hepatobiliary system (e.g., ^{18}F-PSMA-1007), splenic parenchyma is used as the reference tissue instead of the liver. Then, the expression score is evaluated alongside MRI or CT data: prostate tumor presence and extent, soft-tissue lesions in the prostatectomy bed, and structural changes in lymph nodes and bones. The final PET/CT or PET/MRI result is categorized as positive, negative, or equivocal. The miTNM classification mirrors the traditional TNM system, but includes subcategories for distant metastases: unifocal, oligometastatic, disseminated, and diffuse bone marrow involvement. The PSMA-RADS scale, such as PI-RADS, is a 5-point system:

- Scores 1 and 2: benign findings
- Score 3: indeterminate, requiring follow-up or biopsy
- Scores 4 and 5: malignant.

We recommend using PSMA-RADS to assess the possibility of PCa metastases, but not for intraprostatic lesions, for which PI-RADS and biopsy results remain the standard. Final reports should include the miTNM category and individual lesion ratings if less than five lesions are identified [96].

CONCLUSION

Biochemical recurrence of PCa occurs in 25%–50% of patients following radical treatment. However, it impacts cancer-specific survival only in those with established risk factors. Conventional imaging techniques can detect local recurrence and distant metastases. However, their diagnostic sensitivity is directly dependent on PSA concentration.

Hybrid imaging such as PSMA-ligand PET/CT and PET/MRI demonstrate significantly superior diagnostic performance compared with all other available imaging techniques. These modalities enable early detection of local recurrence and regional and distant metastases. They are critical in patients with biochemical recurrence following radical prostatectomy who are at high risk for recurrence and progression. These patients typically start treatment at low PSA levels, at which point, conventional imaging and biopsy often fail to identify recurrence or metastases.

Determining local recurrence and regional and distant metastases with PSMA-ligand PET/CT and PET/MRI prior to salvage radiotherapy allows for modification of the radiation field and enables metastasis-directed therapy in cases of oligometastatic disease or systemic therapy in polymetastatic cases. This diagnostic and treatment strategy improve recurrence-free, cancer-specific, and overall survival and enhance patients' quality of life.

Pelvic mpMRI provides high sensitivity and specificity for detecting local recurrence post-radiotherapy and is essential for lesion localization prior to biopsy. The use of hybrid PET/MRI or PET/CT combined with mpMRI, particularly when imaging results are concordant, allow for omission of biopsy in this patient group.

In candidates for radical therapy following radiotherapy, metastatic disease should be excluded beforehand. Additionally, among patients with biochemical recurrence and at high risk for progression, identifying those with oligometastatic disease is crucial, as they may benefit from stereotactic metastasis-directed radiotherapy. These diagnostic goals are achieved with hybrid PSMA-ligand PET/CT and PET/MRI.

In detecting bone and visceral metastases in PCa, the diagnostic performance of PSMA-ligand PET/CT and PET/MRI is comparable; however, PET/MRI demonstrates slightly higher sensitivity in identifying local recurrence and regional lymph node metastases. Nonetheless, considering the limited number of scientific studies directly comparing these imaging modalities and the small patient cohorts in most available studies, further research is warranted.

ADDITIONAL INFORMATION

Funding source. This article was not supported by any external sources of funding.

Disclosure of interests. The authors declare that they have no relationships, activities or interests (personal, professional or financial) with third parties (commercial, non-commercial, private) whose interests may be affected by the content of the article, as well as no other relationships, activities or interests over the past three years that must be reported.

Authors' contribution. T.M. Rostovtseva: collection and processing of literary data, analysis of the obtained data, writing the manuscript; M.B. Dolgushin: concept of the work, discussion and approval the final version of the manuscript; M.A. Karalkina: collection and processing of literary data; O.A. Koroid: analysis of literary data, discussion and approval the final version of the manuscript; V.E. Sinitsyn: concept of the work, discussion and approval the final version of the manuscript. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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